UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,393	07/30/2001	Ira Pastan	15280-3721US	5265

7590 03/21/2007

KLARQUIST SPARKMAN, LLP
ONE WORLD TRADE CENTER SUITE 1600
121 SW SALMON STREET
PORTLAND, OR 97204-2988

EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/763,393
Filing Date: July 30, 2001
Appellant(s): PASTAN ET AL.

SUSAN ALPERT SIEGEL

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 11, 2006 appealing from the Office action mailed May 16, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

(i) Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 remain rejected under 35 USC 101, Utility.

(ii) Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57, and not claims 1-8,14-15, 17-18, 53-57 as stated in the brief, on page 3, remain rejected under 35 USC 112, first paragraph, enablement.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

35 USC § 112, first paragraph, written description rejection of claims 1-2, 4, 6-8, 14-15, 17-18, 54-57.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Boon T. "Toward a genetic analysis of tumor rejection antigens". Adv Can Res , Vol. 58 (1992), pages 177-210.

Brennan et al. "Cytokine production in culture by cells isolated from the Synnovial membrane". Journal of Autoimmunity, vol. 2 suppl. (1989), pp. 177-186.

Eriksson et al. "Insulin resistance in type 2 (non-insulin-dependent) diabetic patients and their relatives is not associated with defect in the expression of the insulin-responsive glucose transporter (GLUT-4) gene in human skeletal muscle". Diabetologia, vol. 35 (1992), pp. 143-147)

Ezzell. "Cancer vaccines: An idea whose time has come?". J. NIH Res,Vol. 7 (1995), pp. 46-49.

Fu et al. "Translational regulation of human p53 gene expression". EMBO Journal, Vol. 15, (1996), pp. 4392-4401.

Guo et al. "Induction profile of rat organic anion transporting polypeptide 2 (oatp2) by prototypical drug-metabolizing enzyme inducers that activate gene expression through ligand-activated transcription factor pathways". Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212.

Hell et al. "Hodgkin cells accumulate mRNA for bcl-2". Laboratory Investigation, Vol. 73, No. 4 (1995), pp. 492-496.

Kirkin et al. "Melanoma-associated antigens recognized by cytotoxic T lymphocytes", APMIS, Vol. 106 (1998), pp. 665-679.

Smith RT. "Cancer and the immune system". Clin Immunol, Vol. 41, No.4, (1994), pp. 841-849.

Spitler L.E. "Cancer vaccines: The interferon analogy". Cancer Biotherapy, Vol. 10, No.1, (1995), pp. 1-3)

White et al. "Antibody-targeted immunotherapy for treatment of malignancy". Ann Rev Med, Vol. 52 (2001), pp. 125-145

Yokota, J et al. "Altered expression of the retinoblastoma (RB) gene in small-cell carcinoma of the lung". Oncogene, Vol.3 (1988), pp. 471-475.

Zimmer D.B. "Examination of the calcium-modulated protein S100 alpha and its target proteins in adult and developing skeletal muscle. Cell Motility and the Cytoskeleton, vol. 20 (1991), pp. 325-337.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101, Utility

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The specification discloses that the polynucleotide encoding SEQ ID NO:1 is underexpressed, and is **barely detectable** in prostate cancer as compared to normal prostate (figure 4 and p.16), and is overexpressed in uterine cancer as compared to normal uterine (Figure 2B and p.16). The specification further discloses that the predicted PAGE-4 polypeptide of SEQ ID NO:1 has similarity with some amino acids of MAGE5, GAGE and other PAGEs (figure 1). However, there is no data or objective evidence in the specification that the polypeptide SEQ ID NO:1 is **differentially** expressed in prostate or uterine cancer tissue as compared to normal corresponding tissue.

The specification contemplates treating of cancer, using the claimed polypeptide SEQ ID NO:1 or immunogenic portions thereof (p.17-24). The specification contemplates determining motifs or peptides that that binds to MHC I, using computer program known in the art. The specification discloses that given some similarity with MAGE proteins, it is expected to use the procedure for MAGE-2 or MAGE-3 to find and test potential CTL epitopes for PAGE-4 for use in vaccines and ex vivo uses (p.20-25, especially p.22, lines 24-28, p. 24-25). In a Declaration by Dr. Pastan, a CTL peptide, amino acids 16-32 of SEQ ID NO:1 is identified, which peptide induces in vitro CTL lysis of a prostate cancer cell line. However, other than amino acids 16-32

of SEQ ID NO:1, there is no data, or objective evidence that any of the 8 to 11 fragments of SEQ ID NO:1 that bind to MHC actually could induce CTL response. Further, there is no data or objective evidence that the polypeptide SEQ ID NO:1, or any fragments of SEQ ID NO:1, including amino acids 16-32 could be used successfully for treating cancer.

The specification discloses that the peptide of SEQ ID NO:16 could be used for generating antibodies. However, there is no indication that the antibody is specific for SEQ ID NO:1, in view of the disclosed similarity of SEQ ID NO:1 and known polypeptides, such as MAGE, GAGE or other PAGE polypeptide. Nor is there disclosure that said peptide activates the cytotoxic T cells (CTLs). It is noted that a peptide binds to B cells for producing antibodies.

The specification lacks specific and substantial utility, because one cannot determine that the claimed polypeptide SEQ ID NO:1 could be used successfully for diagnosis or treatment of cancers, as contemplated in the specification. Further experimentation is required to determine what the use is for the claimed polypeptide SEQ ID NO:1 or its fragments of 8 to 11 amino acids that bind to MHC.

A) One cannot determine that SEQ ID NO:1 or its fragment could be used successfully for **diagnosis** of cancers that express SEQ ID NO:1, because, although the polynucleotide encoding SEQ ID NO:1 is differentially expressed in prostate and uterine cancers as compared to normal controls, one cannot predict that the encoded SEQ ID NO:1 is also **differentially** expressed in prostate and uterine cancers as compared to normal controls, in view that protein levels cannot be predictably correlated with steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that

levels of the TNF alpha protein were undetectable. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. Similarly, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from cancer patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. This is also confirmed in carcinoma, as shown in the teaching of Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475), who teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to predict levels of protein expression. In view of the teaching in the art, one of skill in the art cannot predict that the level of the specific mRNA

encoding SEQ ID NO:1 will be paralleled at the encoded protein level due to complex homeostatic factors controlling translation and post-translational modification.

B) Further, one cannot determine that SEQ ID NO:1 or its fragments that bind to MHC, including the CTL peptide, amino acids 16-25 of SEQ ID NO:1 could be used successfully for **cancer treatment**, because cancer immunotherapy is unpredictable. Further experimentation is required to determine what the use is for the claimed polypeptides of SEQ ID NO:1 or its fragments of 8 to 10 or 11 amino acids that binds MHC I. Kirkin et al, 1998, APMIS, 106 : 665-679, review in vivo efficacy of CTL peptides of families of cancer specific antigens, such as MAGE, including MAGE-1, MAGE-2, and MAGE-3, BAGE, GAGE, PRAME and NY-ESO, and melanoma-associated antigens, such as MART-1, gp100, TRP-1, and TRP-2, having peptides recognized by CTLs (abstract, table 1 on page 667). Kirkin et al conclude that although several CTL peptides have been tested in vivo, so far only two patients response to these peptide antigens in vivo, and that in particular, for CTL peptides of the MAGE families, **only one** peptide, EVDPIGHLY of MAGE-A3, has limited **anti-tumor** activity, indicating their low immunogenicity (Kirkin et al, abstract, and especially p.666, second column, second paragraph, last 6 lines). Further, even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al, 1992, Adv Can Res , 58:177-210 (see p. 194-198, 203-204). Boon further teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to

respond against the tumor (p. 206, para 2). In addition, problem with tumor tolerance and the loss of surface Class I MHC is well known. For example, Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Further, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Thus in view of the teaching in the art, one cannot predict that the polypeptide SEQ ID NO:1 or fragments thereof, including the CTL peptide P16 could be used

for treating prostate cancer. Further experimentation is required to determine what use is for the polypeptide SEQ ID NO:1, or fragments thereof, including the CTL peptide P16.

Further, even CTLs could be activated in vitro and lyse a prostate cancer cell line by SEQ ID NO:1 protein, or the CTL peptide P16 thereof, one cannot predict whether said CTLs would recognize and lyse cancer cells in vivo, such as prostate cancer cells in vivo, due the unpredictability of sufficient quantity of the protein expressed on the surface of the primary cancer cells, especially when the cDNA encoding SEQ ID NO:1 is barely detectable in prostate cancer tissue as compared to normal prostate tissue. This possible problem with insufficient quantity of SEQ ID NO:1 expressed on malignant cells could further be exacerbated, in view that cancer cells could downregulate the expression of tumor antigens, and thus reducing the amount of the antigens presented, and consequently the possibility of being recognized and lysed by CTLs, and further in view of the well-known cancer tolerance phenomena. For example, White et al, 2001, Ann Rev Med, 52: 125-145, teach that antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last).

Neither the specification nor any art of record teaches what the polypeptide is, what it does. The specification does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments other than the peptide P16 might be CTL epitopes and would function as claimed.

In the absence of any disclosed relationship between the claimed polypeptide or fragments thereof and any disease or disorder and the lack of any correlation between the claimed polypeptide or fragments thereof with any known disease or disorder, and further in view that

any potential diagnostic or therapeutic utility is not yet known and has not yet been disclosed, the utility is not substantial. Further research is necessary to determine what use is for the claimed polypeptide or fragments thereof. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

For reasons set forth above the disclosure satisfies none of the three criteria of a specific, substantial, and credible utility. *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112 First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 also rejected under 35 U.S.C. 112, first paragraph.

A) Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

B) Further, claims 15, 18 encompasses a method for treating a cancer cell expressing SEQ ID NO:1, using a genus of 8 to 11 amino acids fragments of SEQ ID NO:1 that bind to MHC I as claimed in claims 1, 4, 6, 54, 55, 57. However, other than the CTL peptide 16, or amino acids 16-25 of SEQ ID NO:1, as disclosed in the Declaration by Dr. Pastan, one cannot predict **which** other peptides of SEQ ID NO:1 that bind to MHC I could be used for the claimed method of cancer treatment, because not any peptides that bind to MHC have the ability to induce CTL lysis of target cells, a property necessary for their potential use in cancer treatment. For example, Kirkin et al teach that although the specific peptide 27-35 of Melan-A/MART-1 induce CTL response in vitro, other Melan-A/MART-1 peptides having **higher affinity** to the HLA-A2.1 do not induce the generation of melanoma-specific CTL (p.670, first column, last paragraph, bridging second column, and especially lines 9-20).

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

C) In addition, claims 14-15, 17-8 encompass a method for treating **any** malignant cells that express SEQ ID NO:1.

Not only one cannot predict that prostate or uterine cancer tissue differentially expresses SEQ ID NO:1 as compared to normal non-cancerous corresponding tissue, supra, one cannot predict that any other cancer also differentially expresses SEQ ID NO:1, and could be successfully treated by the claimed method, because expression level of a protein in a cancer is not predictable, and because different cancers have different etiology and characteristics, and their response to treatment is not predictable.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

(10) Response to Argument

Claim Rejections - 35 USC § 101, Utility

Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The response asserts that the specification discloses that the polypeptide SEQ ID NO:1 and fragments thereof of 8 to 11 contiguous amino acids are of use to (1) detect and (2) treat cancer, such as prostate cancer. The response asserts that this use is "specific" for claimed polypeptides, is "substantial" as is the "real world" use of cancer treatment, and is "credible" as the production of an immune response against tumor antigens is known to be of use for cancer

treatment. The response asserts that this is evidenced by Visseren et al, which teaches that peptides predicted to bind MHC generally were immunogenic, and suggests that epitope based vaccines including some of the predicted peptide sequences can be used for prevention and treatment of tumors (see Visseren et al., page 129).

The response has been considered but is not found to be persuasive for the following reasons:

The claimed invention is not supported by either a specific asserted utility or a well established utility for the following reasons: 1) One cannot determine that the claimed polypeptide SEQ ID NO:1 is **differentially** expressed in cancer tissues, such as prostate or uterine cancer, as compared to the control non-cancerous corresponding tissues, such that the claimed polypeptide SEQ ID NO:1 or a fragment thereof, could be used for **diagnosis** of cancers, such as prostate or uterine cancer, and 2) One cannot determine that the claimed polypeptide SEQ ID NO:1, or its fragment, such as the P16 CTL epitope peptide, or amino acids 16-25 of SEQ ID NO:1, as identified in the Declaration by Dr Patan on 12/11/06, could be used for **treating** cancers, such as prostate or uterine cancer. Because the claimed invention is not supported by a specific, substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Concerning the response's reference to Visseren et al, 1997, there is no indication, nor any data in Visseren et al that the MAGE-2 CTL peptides identified by Visseren et al actually are successfully used for treating cancers, including prostate or uterine cancers. On the contrary, based on the teaching of Kirkin et al, Boon, Smith et al, Ezzell, Spitler, and White et al, one would conclude that one cannot predict that any CTL peptides, and in particular MAGE related

CTL peptides, could be used for treating cancer, unless tested. Visseren et al only teach that seven MAGE-2 CTL peptides were identified and administered into non-cancerous transgenic mice, and that their immunogenicity is shown by **in vitro** lytic activity of spleen cells of said transgenic mice against a cell line transfected with MAGE-2 (Visseren et al, p. 127, first column, item under Immunogenicity of MAGE-2 peptides in transgenic mice, p.129, first column). There is no indication, nor any data in Visseren et al that the MAGE-2 CTL peptides actually are successfully used for treating cancers. However, later, in 1998, Kirkin et al review in vivo efficacy of CTL peptides of families of cancer specific antigens, such as MAGE, including MAGE-1, MAGE-2, and MAGE-3, and the two most promising MAGE-2 peptides disclosed by Visseren et al, KMVELVHFL, and YLQLVFGIEV (Visseren et al, page 129, first column, last paragraph), and BAGE, GAGE, PRAME and NY-ESO, and melanoma-associated antigens, such as MART-1, gp100, TRP-1, and TRP-2, having peptides recognized by CTLs (abstract, table 1 on page 667). Kirkin et al conclude that although several CTL peptides have been tested in vitro, so far only two patients response to these peptide antigens in vivo, and that in particular, for CTL peptides of the MAGE families, so far **only one** peptide, EVDPIGHLY of MAGE-A3, has limited **anti-tumor** activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, abstract, and especially p.666, second column, second paragraph, last 6 lines). In view of the above teaching of Kirkin et al, and further in view that cancer treatment is unpredictable, as taught by Boon, Smith et al, Ezzell, Spitler, and White et al, supra, one cannot predict that the claimed PAGE-4 polypeptide SEQ ID NO:1, which has some similarity with MAGE-5, GAGE and other PAGE, as disclosed in the specification, figure 1, or a fragment of

SEQ ID NO:1 that binds to MHC I, such as the P16 CTL peptide, or amino acids 16-25 of SEQ ID NO:1, could be used for **treating** cancer, such as prostate or uterine cancer

1. One cannot determine nor predict that the claimed polypeptide SEQ ID NO:1 is differentially expressed in prostate or uterine cancer tissue as compared to normal prostate or uterine tissue, such that the claimed polypeptide or its fragment could be used for detecting prostate or uterine cancer.

The response asserts on pages 15-16 that the level of protein is correlated with that of the encoding gene. The response asserts that in contrast to the teaching of Brennan et al, Zimmer et al, Eriksson et al, Hell et al, Guo et al, Fu et al and Yokota, cited by the Examiner, Ornoft et al describes a genome-wide study of gene copy numbers, transcripts and protein levels in pairs of non-invasive and invasive human carcinomas. The response asserts that although it was only possible to compare mRNA and protein in a few cases (due to a limited ability to focus some of the proteins on two dimensional gels), Ornoft et al teach that there was a good correlation (p0.005) between transcript alterations and protein levels. The response asserts that Omtoft et al. continue to describe a limited set of genes wherein mRNA and protein do not correlate (this is the seven genes referred to on page 11 of the final Office action), and that, however, Omtoft et al. conclude that the lack of correlation between these specific mRNAs and proteins is related to the location of these genes on chromosome 17 (see page 43 of Ornoft et al.). The response concludes that thus, for other proteins (not belonging to this specific family encoded by chromosome 17) protein expression uniformly correlated to mRNA level. The response asserts that thus, the results presented in Ornoft et al. support the conclusion that a showing of a

correlation between mRNA level and the presence of cancer is sufficient to support the association of the expression of a protein with the presence of cancer.

The response has been considered but is not found to be persuasive for the following reasons:

It is noted that the specification discloses that the **cDNA** encoding SEQ ID NO:1 is **under**expressed in prostate cancer, and is **barely detected** in prostate cancer tissue, as compared to normal prostate cancer (figure 4 and page 16), and is overexpressed in uterine cancer as compared to normal uterine (figure 2B and page 16). The specification and the Declaration by Dr Pastan et al however do not have any data concerning the expression level of the encoded protein SEQ ID NO:1 in prostate or uterine cancer tissue as compared to control prostate or uterine tissue from healthy individual. Further, in a post filing reference submitted by Appellant, Iavarone et al teach that the PAGE-4 protein is expressed in **both** normal and prostate cancer (abstract,). However, there is no indication in Iavarone et al that the PAGE-4 protein is **differentially** expressed in prostate cancer tissue as compared to normal prostate tissue.

Concerning Ornoft et al, the data in Ornoft et al is misinterpreted in the response. Ornoft et al do not teach that the lack of correlation between the 7 specific mRNAs and proteins is related to the location of these genes on chromosome 17. Contrary to the response assertion, one would conclude from the teaching of Ornoft et al that some of those 19 genes that show correlation between mRNA and protein levels belong to chromosome 17 (see Table II, item under chromosomal location, on page 43). Although Ornoft et al intended to compare gene copy numbers, transcripts and protein levels in a genome-wide study in pairs of non-invasive and invasive human carcinomas, actually only 26 genes were analyzed due to a limited ability to

focus some of the proteins on two dimensional gels. From 26 genes studied, 19 genes shows correlation between mRNAs and protein levels; however, **7 genes do not** have any correlation between mRNAs and protein levels. Further, Orntoft et al teach that except for a groups of cytokeratins encoded by genes from chromosome 17, the analyzed proteins did not belong to a particular family (p.42, last line, bridging p.43). It is noted that cytokeratins shows a correlation between mRNA and protein levels (table II on page 43). Orntoft et al teach that from 11 genes showing a significant correlation between mRNAs level and their encoded protein levels, four are genes located at the frequently amplified area of chromosome 17q (p.45, first column, first paragraph). Orntof et al goes on and teach that study of mechanisms of alteration of these proteins is complicated by modification that occurs after translation (p.45, first column, first paragraph). Thus, contrary to the response assertion, one would conclude from the teaching of Orntoft et al that some of those 19 genes that show correlation between mRNA and protein levels belong to chromosome 17 (see Table II, item under chromosomal location, on page 43). Further, since 7 genes from a total of 26 genes do not show correlation between mRNAs and protein levels, as taught by Orntoft et al, one would conclude that **which protein has a correlation with that of the encoding mRNAs cannot be predicted.** There are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA. Further, proteins may differ substantially in their *in vivo* half lives. In addition, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. This is confirmed by the following overwhelming teaching in the art. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels

of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-ranslational level. Similarly, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401), who teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from cancer patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. This is also confirmed in carcinoma, as shown in the teaching of Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475), who teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to extrapolate to levels of protein expression.

The response asserts on page 16 that the Declaration of Dr. Pastan describes that Northern blot and reverse transcriptase polymerase chain reaction (see the specification, page 4, line 30 to page 5, line 6; page 5, lines 16-20; and FIGS. 3 and 5) were used to evaluate the expression of PAGE4 in prostate cancer, and that polyclonal antibodies (see Example 3, page 41 of the specification) were used to demonstrate that PAGE4 protein (SEQ ID NO: 1) was expressed in prostate cancer. The response asserts that Western blot analysis by Iavrone et al, 2002, confirmed that PAGE4 protein was expressed in a prostate cancer lysate (see Fig. 2B of Iavrone et al., Mol. Cancer Therap. 1: 329-335, 2002, of record, for an exemplary blot). The response asserts that , for PAGE 4, there is a 100% correlation between mRNA expression and protein expression. The response concludes that this specific data with respect to the expression of PAGE4 (SEQ ID NO: 1) negates any general allegations of inoperability based on the prior art describing the expression of unrelated genes. The response concludes that this specific data documents that polypeptides comprising SEQ ID NO: 1 can be used to detect prostate cancer.

The response has been considered but is not found to be persuasive for the following reasons:

There is no data in the Declaration by Dr. Pastan concerning the level of expression of the polypeptide SEQ ID NO:1 in prostate cancer tissue as compared to normal prostate tissue. Because of this, one cannot assess the level of the polypeptide SEQ ID NO:1 in prostate cancer tissue as compared to normal prostate tissue, based on the Declaration.

Further, there is no indication in the reference by Iavrone et al that the polypeptide SEQ ID NO:1 is differentially expressed in prostate cancer tissue as compared to normal prostate tissue. The submitted reference by Iavarone et al discloses that PAGE 4 protein is expressed in

both normal and prostate cancer (abstract, p.332, first column). The text in Iavarone et al does not state that the PAGE4 protein is differentially expressed in prostate cancer tissue as compared to normal prostate tissue. Further, the levels of the PAGE 4 protein in figure 3 of the submitted Iavarone et al reference could not be determined, because the gel picture in figure 3 is unclear.

Moreover, the PAGE 4 mRNA expression level disclosed in Iavarone et al, and as asserted in the Declaration by Dr.Pastan is **contradictory** with that disclosed for PAGE 4 cDNA encoding SEQ ID NO:1 in the instant specification. Iavarone et al teach that PAGE4 mRNA is **highly expressed** in both normal prostate and prostate cancer tissue (p.331, second column), whereas the PAGE4 SEQ ID NO:1 is almost **undetectable** in prostate cancer tissue as compared to normal prostate in the instant specification (figure 4). Because of this contradiction, one cannot determine whether the claimed PAGE 4 SEQ ID NO:1 is **the same** as the PAGE 4 cDNA and the encoding protein thereof disclosed in Iavarone et al.

Thus, in view that a lack of any objective evidence that the polypeptide SEQ ID NO:1 is differentially expressed in prostate cancer tissue as compared to normal prostate tissue, and in view that the level of expression of a polypeptide in cancer is unpredictable, one cannot predict that the claimed polypeptide SEQ ID NO:1 could be used for detecting prostate cancer. Further experimentation is required to determine whether the polypeptide SEQ ID NO:1 could be used for detecting prostate cancer.

2. *One cannot determine nor predict that the claimed polypeptide SEQ ID NO:1 or fragments thereof could be used for treating cancer.*

The response asserts on page 16, last paragraph, bridging page 17 that in the Declaration by Dr. Pastan, two peptides of SEQ ID NO:1 binds HLA-A2 with high affinity, and one of these peptides, P16, could activate CTLs, that lyses prostate tumor cells that expresses PAGE-4 (SEQ ID NO:1). The response concludes that thus the data supports a utility, the production of an immune response to prostate cancer cells, for the claimed polypeptide.

The response has been considered but is not found to be persuasive for the following reasons:

It is noted that there is no data in the Declaration of Dr. Pastan concerning in vivo prostate cancer treatment by the CTL peptide P16. The Declaration by Dr. Pastan only discloses that the CTL peptide P16 activates T cells generated ***in vitro*** from peripheral blood mononuclear cells of prostate cancer patients (p.3-4, table 2 on page 4), and that the CTLs lyse ***in vitro*** a prostate cancer cell line LNCaP, expressing PAGE-4 polypeptide SEQ ID NO:1 (table 3 on page 5, and page 5, last paragraph).

However, one cannot extrapolate from activation of CTLs which could lyse a prostate cancer cell line in vitro to in vivo treatment of prostate cancer, using the claimed polypeptide or its CTL peptide P16, because cancer immunotherapy is highly unpredictable. Kirkin et al review in vivo efficacy of CTL peptides of families of cancer specific antigens, such as MAGE, including MAGE-1, MAGE-2, and MAGE-3, BAGE, GAGE, PRAME and NY-ESO, and melanoma-associated antigens, such as MART-1, gp100, TRP-1, and TRP-2, having peptides recognized by CTLs (abstract, table 1 on page 667). Kirkin et al conclude that although several

CTL peptides have been tested in vivo, so far only two patients response to these peptide antigens in vivo, and that in particular, for all the reported CTL peptides of the MAGE families, **only one** peptide, EVDPIGHLY of MAGE-A3, has limited **anti-tumor** activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, abstract, and especially p.666, second column, second paragraph, last 6 lines). Further, even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al (p.194-198, 203-204). Boon further teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, problem with tumor tolerance and the loss of surface Class I MHC is well known. For example, Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Further, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on

which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1). Thus in view of the teaching in the art, one cannot predict that the polypeptide SEQ ID NO:1 or fragments thereof, including the CTL peptide P16 could be used for treating prostate cancer. Further experimentation is required to determine what use is for the polypeptide SEQ ID NO:1, or fragments thereof, including the CTL peptide P16.

The response recites case laws on pages 18-21, and asserting that Appellant only needs to document a reasonable correlation between activity and asserted use. The response asserts that Boon's teaching of failure of one particular therapy of cancer does not negate an asserted therapeutic use of all other therapies. The response asserts that the final Office action assertion that the Declaration of Dr. Pastan shows only in vitro data, and that this cannot be used to support or predict the use of PAGE-4 peptides to treat cancer contradicts the teaching of MPEP 2107.03. The response asserts that MPEP2107 confirms that in vitro data can be used to support an asserted utility, and that even in situations where there are no previously successful

treatments, there is no basis for a utility rejection, except in those cases where the applicant was unable to come forward with any relevant evidence to rebut the finding by the Office. The response asserts that this is evidenced by Visseren et al, which teach that peptides from a related polypeptide, MAGE –2 can be used to produce an immune response against melanoma cells. The response recites *In re Jollies*, asserting that one would predict that the therapeutic utility of the claimed peptides is credible.

The response has been considered but is not found to be persuasive for the following reasons:

MPEP2107 teach that "if reasonably correlated (emphasis added) to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process". In the instant application, there is no reasonable correlation between in vitro lysis of a prostate cancer line by the claimed CTL peptide P16 and its in vivo use in treating cancer, including prostate or uterine cancer, in view of Kirkin et al, Boon, Smith et al, Ezzell, Spitler, which teach the unpredictability of different types of therapy of cancer, supra.

Moreover, concerning the CTL peptides taught by Vissera et al, it is noted that Kirkin et al review in vivo efficacy of CTL peptides of families of cancer specific antigens, such as MAGE, including MAGE-1, MAGE-2, and MAGE-3, and the two most promising MAGE-2 peptides disclosed by Visseren et al, KMVELVHFL, and YLQLVFGIEV (Visseren et al, page 129, first column, last paragraph), and BAGE, GAGE, PRAME and NY-ESO, and melanoma-associated antigens, such as MART-1, gp100, TRP-1, and TRP-2, having peptides recognized by

CTLs (abstract, table 1 on page 667). Kirkin et al conclude that although several CTL peptides have been tested in vitro, so far only two patients response to these peptide antigens in vivo, and that in particular, for CTL peptides of the MAGE families, so far **only one** peptide, EVDPIGHLY of MAGE-A3, has limited **anti-tumor** activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, abstract, and especially p.666, second column, second paragraph, last 6 lines). In view of the above teaching of Kirkin et al, and further in view that cancer treatment is unpredictable, as taught by Boon, Smith et al, Ezzell, Spitler, and White et al, supra, one cannot predict that the claimed PAGE-4 polypeptide SEQ ID NO:1, which has some **similarity** with MAGE-5, GAGE and other PAGE, as disclosed in the specification, figure 1, or the claimed PAGE-4 fragment, including the CTL peptide P16, amino acids 16-25 of SEQ ID NO:1, could be used for **treating** cancers, such as prostate or uterine cancer.

Thus, the disclosure satisfies none of the three criteria of a specific, substantial, and credible utility. *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide or fragments thereof. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112 First Paragraph, Enablement

Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 remain rejected under 35 U.S.C. 112, first paragraph, because the claimed invention is not supported by specific, substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, and one skilled in the art clearly would not know how to use the claimed invention.

The response asserts on page 29 that since the final Office action does not appear to address claim 54, which is directed to a polypeptide consisting of SEQ ID NO:1, and since SEQ ID NO:1 is provided by the specification, claim 54 is fully enabled.

The response has been considered but is not found to be persuasive for the following reasons:

It is noted that contrary to the response assertion, in the final office action, on pages 19-27, and similarly in this Office action, all the pending claims 1-2, 4, 6-8, 14-15, 17-18, 53-57, which clearly include claim 54, are rejected for being not enabled, because one would not know how to use the claimed polypeptides and methods of treatment of a cancer that expresses SEQ ID NO:1.

The followings are the Wands analysis:

The breath of the claims.

The response asserts that:

1) The claims 1, 2, 7 and 53 are limited to polypeptides comprising SEQ ID NO:1,

2) The claims 2, 4, 6, 8 and 55-57 are limited to fragments of eight to eleven amino acids of SEQ ID NO:1, i.e. a single amino acid sequence of 102 amino acids, that can bind to MHC,

3) The claim 54 is directed to a polypeptide consisting of SEQ ID NO:1, and

4) The claims 14-15, 17-18 are directed to the use of the claimed polypeptides to inhibit growth of a malignant cell by activating cytotoxic T lymphocytes (CTLs).

The response has been considered but is not found to be persuasive for the following reasons:

1) Claims 1, 2, 7, 53, 56, and **not** claims 1, 2, 7, and 53, as asserted in the brief, are directed to the polypeptide comprising SEQ ID NO:1.

2) Claims 1, 4, 6, 8, 54-55, 57, and **not** claims 2, 4, 6, 8 and 55-57 as asserted in the brief, are directed to fragments of eight to eleven amino acids of SEQ ID NO:1 that bind MHC I.

The scope of the claims are broad, in view that except the CTL peptide amino acids 16-25 of SEQ ID NO:1 disclosed in the Declaration by Dr. Pastan, one cannot predict which of the other 8 to 11 amino acid fragment of SEQ ID NO:1 that binds to MHC I has the ability to induce CTL lysis of target cells, a property necessary for its potential use in the claimed method of treating cancer.

3) Claim 54 is directed to a polypeptide consisting of 8 to 11 contiguous amino acids of SEQ ID NO:1, supra, and is **not** directed to a polypeptide consisting of SEQ ID NO:1, as asserted in the brief.

4) Claims 14-15, 17-18 are directed to a method for **treating any cancers**, provided they express SEQ ID NO:1, using:

a) the claimed polypeptide SEQ ID NO:1,

b) **any** peptide fragment thereof consisting of 8 to 11 contiguous amino acids that bind to MHC I, or

c) CTLs activated by SEQ ID NO:1, or by **any** peptide fragment thereof consisting of 8 to 11 contiguous amino acids that bind to MHC I.

The scope of the claims are broad, in view that one cannot predict whether the claimed polypeptide SEQ ID NO:1, or any fragments thereof that bind to MHC I, or the CTL epitope P16, amino acids 16-25 of SEQ ID NO:1, could be used successfully for treating cancers expressing SEQ ID NO:1.

The nature of the invention.

The response asserts that the nature of the invention is limited to: 1) the amino acid sequence comprising SEQ ID NO:1, 2) a polypeptide consisting of 8 to 11 amino acids of SEQ ID NO:1 that bind to MHC, and 3) the use of these polypeptides to inhibit growth of malignant cells expressing SEQ ID NO:1, thus concerning activation of the immune system with the specific polypeptide. The response asserts that methods for synthesizing the sequences are routine and/or automated.

The response has been considered but is not found to be persuasive for the following reasons:

The nature of the invention is complex. The Examiner agrees that the invention are related to: 1) the amino acid sequence comprising SEQ ID NO:1, 2) a polypeptide consisting of 8 to 11 amino acids of SEQ ID NO:1 that bind to MHC, and 3) the use of these polypeptides to inhibit growth of malignant cells expressing SEQ ID NO:1.

However, although the specification provides the structure of the full length SEQ ID NO:1, and although methods of synthesizing sequences are routine in the art, except the CTL peptide amino acids 16-25 of SEQ ID NO:1 disclosed in the Declaration by Dr. Pastan, one cannot predict which of the 8 to 11 amino acid fragment thereof that binds to MHC I has the ability to induce CTL lysis of target cells, a property necessary for its potential use in the claimed method of treating cancer. Further, whether SEQ ID NO:1 or 8 to 11 amino acid fragments thereof that bind to MHC I, including the CTL epitope P16, amino acids 16-25 of SEQ ID NO:1, can be used for detecting or treating cancers expressing SEQ ID NO:1 is not predictable.

The state of the prior art.

(a) The response asserts that a protein such as PAGE 4 (SEQ ID NO:1) can be chemically synthesized by standard method, or by well known recombinant method.

(b) The response asserts that computer program exists that will predict which nine consecutive amino acids will bind to MHC, and that pharmaceutical formulation of immunogenic compositions and administration of polypeptides as pharmaceutical compositions are well known in the art.

(c) The response asserts that the use of immunogenic peptides to inhibit growth of malignant cell is well known in the art, as evidenced by Visseren et al, who describes the use of MAGE protein for the treatment of melanoma.

The response has been considered but is not found to be persuasive for the following reasons:

(a) Although PAGE-4 polypeptide SEQ ID NO:1 can be routinely synthesized or made recombinantly, there are no data in the specification, or the art showing, nor one can predict that SEQ ID NO:1 could be successfully used for detecting or treating cancer, including prostate or uterine cancer.

(b) Further, although computer program exists that will predict which nine consecutive amino acids will bind to MHC, however, other than the CTL epitope P16, one cannot predict which other nine consecutive amino acids that bind to MHC could induce CTL lysis of target cells, a property necessary for their potential use in the claimed method of treating cancer.

(c) There are no data in the specification or in the art showing, nor one can predict that the specific polypeptide SEQ ID NO:1 or any of its 8 to 11 fragments thereof that bind to MHC could be successfully used for inhibiting growth of cancer cells that express SEQ ID NO:1.

In addition, although the use of some immunogenic peptides to inhibit growth of malignant cell is well known in the art, not any immunogenic peptides could be predictably successfully used for inhibiting growth of malignant cells, in view of the teaching of Kirkin et al, Boon, Smith et al, Ezzell et al, and Spitler, supra, which teach the unpredictability of immunotherapy.

The level of skill of one of ordinary skill in the art.

The response asserts that the level of skill of the average molecular biologist or immunologist is high.

The Examiner takes note that although the level of skill in the field of molecular pathology is high, however, it would be undue experimentation for one of skill in the art to practice the claimed invention, due to the high level of unpredictability concerning detecting and treating cancer, using the polypeptide SEQ ID NO:1 or its 8 to 11 fragments thereof that bind to MHC I.

The level of predictability in the art.

1) The response asserts that production of a specified sequence, or its fusion protein, is well known.

2) The response asserts that computer program can be used to predict which eight to ten consecutive amino acids of a specified polypeptide are likely to bind to MHC, and to rank polypeptides in order of predicted strength of the binding. The response asserts that once the polypeptides are identified, a biological assay can be used to confirm that the eight to ten consecutive amino acids actually bind MHC.

3) The response asserts that once the sequence of an immunogenic peptide is determined, the use of that peptide to induce an immune response against a cell expressing SEQ ID NO: 1 is predictable. The response asserts that once the amino acid sequence of a polypeptide is known, that polypeptide can be used to produce activated T cells (Tsang et al., J Natl. Cancer Inst 87:982-90, 1995) that can lyse tumor cells expressing the full-length polypeptide.

The recitation of Tsang et al is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

The level of unpredictability is high.

1) One cannot predict that the claimed polypeptide SEQ ID NO:1 is **differentially** expressed in cancer tissues, including prostate and uterine cancer tissue as compared to corresponding normal control tissue, such that it can be used for **detecting** cancer, for the following reasons: The level of expression of the encoded polypeptide SEQ ID NO:1 cannot be predicted based on the mRNA level of the cDNA encoding SEQ ID NO:1, in view of the teaching of Brennan et al, Zimmer et al, Eriksson et al, Hell et al, and Guo et al, Fu et al, Yokota et al. supra, which recognizes that mRNA level is not predictably an indication of protein production level .

Further, the submitted reference by Iavarone et al discloses that PAGE 4 protein is expressed in **both** normal and prostate cancer (abstract, p.332, first column). There is no indication in Iavarone et al that the PAGE-4 protein is **differentially** expressed in prostate cancer tissue as compared to normal prostate tissue. The text in Iavarone et al does not state that the PAGE4 protein is differentially expressed in prostate cancer tissue as compared to normal prostate tissue. Further, the levels of the PAGE 4 protein in figure 3 of the submitted Iavarone et al reference could not be determined, because the gel picture in figure 3 is unclear.

Moreover, the PAGE 4 mRNA expression level disclosed in Iavarone et al is **contradictory** with that disclosed for PAGE 4 cDNA encoding SEQ ID NO:1 in the instant specification. Iavarone et al teach that PAGE4 mRNA is highly expressed in both normal

prostate and prostate cancer tissue (p.331, second column), whereas the PAGE4 SEQ ID NO:1 is almost undetectable in prostate cancer tissue as compared to normal prostate in the instant specification (figure 4). Because of this contradiction, one cannot determine whether the claimed PAGE 4 SEQ ID NO:1 is the **same** as the PAGE 4 cDNA and the encoding protein thereof disclosed in Iavarone et al.

2) Further, although computer program can be used to predict which eight to ten consecutive amino acids of a specified polypeptide are likely to bind to MHC, binding to MHC by itself is not sufficient to predict which peptides are useful for diagnosis or treatment of cancer, because not **any** peptide that bind to MHC could induce CTLs response, and especially lysis of primary cancer cells in vivo by said CTLs. For example, Kirkin et al teach that although the specific peptide 27-35 of Melan-A/MART-1 induce CTL response in vitro, other Melan-A/MART-1 peptides having **higher affinity** to the HLA-A2.1 do not induce the generation of melanoma-specific CTL (p.670, first column, last paragraph, bridging second column, and especially lines 9-20). Moreover, Kirkin teach that although the specific peptide 27-35 of Melan-A/MART-1 induce CTL response in vitro, immunization with this peptide **does not** induce tumor regression (p.670, second column, last ten lines of the first paragraph).

3) Further, one cannot predict that SEQ ID NO:1 or fragments thereof that binds to MHC I can be used for **treating** cancer, in view that cancer treatment is highly unpredictable. Kirkin et al review in vivo efficacy of CTL peptides of families of cancer specific antigens, such as MAGE, including MAGE-1, MAGE-2, and MAGE-3, and the two most promising MAGE-2 peptides disclosed by Visseren et al, KMVELVHFL, and YLQLVFGIEV (Visseren et al, page 129, first column, last paragraph), and BAGE, GAGE, PRAME and NY-ESO, and melanoma-

associated antigens, such as MART-1, gp100, TRP-1, and TRP-2, having peptides recognized by CTLs (abstract, table 1 on page 667). Kirkin et al conclude that although several CTL peptides have been tested in vitro, so far only two patients response to these peptide antigens in vivo, and that in particular, for CTL peptides of the MAGE families, so far **only one** peptide, EVDPIGHLY of MAGE-A3, has limited **anti-tumor** activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, abstract, and especially p.666, second column, second paragraph, last 6 lines). In view of the above teaching of Kirkin et al, and further in view that cancer treatment is unpredictable, as taught by Boon, Smith et al, Ezzell, Spitler, and White et al, supra, one cannot predict that the claimed PAGE-4 polypeptide SEQ ID NO:1, which has some similarity with MAGE-5, GAGE and other PAGE, as disclosed in the specification, figure 1, or the claimed PAGE-4 fragment, such as the P16 CTL peptide, or amino acids 16-25 of SEQ ID NO:1, as disclosed in the Declaration by Dr. Pastan, could be used for **treating** cancers, such as prostate or uterine cancer.

The amount of direction provided by the application and the existence of working examples

The response asserts that the specification discloses SEQ ID NO:1, and peptides of 8-10 amino acids of SEQ ID NO:1, that have binding motifs for HLA-A2 with specific anchoring residues in second and positively charged amino acid at the position nine. The response asserts that the specification discloses the methods and computer based programs for predicting MHC binding motifs. The response asserts that methods for testing whether a specific epitope is immunogenic is also provided. The response asserts that using the guidance provided by the

specification, CTLs could be produced that lyse malignant cells expressing SEQ ID NO:1, as evidenced by the Declaration of Dr. Pastan. The response asserts that a fragment of PAGE4 (15 amino acids) that can be used to produce antibodies is disclosed on page 41. The response asserts that the use of PAGE 4 peptide to produce an immune response, and the treatment of cancer is disclosed in the specification. The response asserts that similar to *In re Bundy*, the claimed novel peptides have specific pharmacological properties and possess a specific acitivity, i.e. the binding of MHC.

The response has been considered but is not found to be persuasive for the following reasons:

There is insufficient guidance from the specification. The specification does not disclose, nor is there any example, or any objective evidence showing that the polypeptide SEQ ID NO:1 is differentially expressed in primary cancer tissue as compared to normal corresponding control cells, such that the claimed polypeptide, or its fragments that bind to MHC, or the antibody to a fragment of SEQ ID NO:1 could be used successfully for diagnosis of cancer. The specification does not disclose, nor is there any example, or any objective evidence showing that SEQ ID NO:1 or its fragments that bind to MHC I could be used successfully for treating cancer. Further, except one single CTL peptide disclosed in the Declaration by Dr. Pastan that induces **in vitro** lysis of a prostate cancer **cell line**, the specification does not describe which other claimed numerous peptide fragments of SEQ ID NO:1 that bind to MHC class I have the ability to induce CTL lysis of target cells, a property necessary for their potential use in the claimed method of treatment of cancer. Screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, Fed Cir, 2004, that screening assays, and by

inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

The quantity of experimentation needed to make or use the invention.

Applicant argues that very limited routine experimentation is required to produce the polypeptide SEQ ID NO:1. Applicant argues that that a computer program publicly available could be used to identify epitopes that bind MHC, which are then synthesized. Applicant argues that once synthesized, the polypeptides must be screened for its binding to MHC and induction of CTL response, using the methods provided in the specification, as evidence by the Declaration by Dr Pastan and by Tsang et al.

The response has been considered but is not found to be persuasive for the following reasons:

The quantity of experiment to determine whether SEQ ID NO:1, or a fragment thereof, could be successfully used for diagnosis or treating cancer is enormous, and not routine, in view of: 1) the unpredictability of differential expression of the polypeptide SEQ ID NO:1 in primary cancer tissue as compared to normal control tissue, 2) the unpredictability of which 8-11 amino acids peptide from SEQ ID NO:1 that bind to MHC class I has the ability to elicit CTLs lysis of target cells, especially killing primary cancer cells in vivo, and 3) the unpredictability of successful use of SEQ ID NO:1 or a fragment thereof that binds to MHC I for cancer treatment.

Moreover, it is not routine to screen for the claimed peptides that bind to MHC I for use in the claimed method of cancer treatment, in view of the unpredictability of which 8-11 amino acids peptide from SEQ ID NO:1 that bind to MHC class I has the ability to elicit CTLs response, especially killing primary cancer cells in vivo, so that they could be used in the claimed method of treating cancer. Screening assays do not enable the claimed invention because the court found in *Rochester v. Searle*, 358 F.3d 916, Fed Cir, 2004, that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

In summary, given 1) the unpredictability of differential expression of the polypeptide SEQ ID NO:1 in primary cancer tissue as compared to normal control tissue, 2) the unpredictability of which 8-10 amino acids peptide from SEQ ID NO:1 that bind to MHC class I has the ability to elicit CTLs lysis of target cells, especially killing primary cancer cells in vivo, and 3) the unpredictability of the successful use of SEQ ID NO:1, or a fragment thereof that binds to MHC I, for cancer treatment, and in view of the complex nature of the invention, and further in view of insufficient disclosure in the instant specification, and little is known in the art

concerning the claimed invention, it would be undue experimentation for one of skill in the art to practice the claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

MINH-TAM DAVIS, PhD.

Patent Examiner,

March 13, 2007

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conferees:

Shanon Foley, SPE

Larry Helms, SPE

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER